

REMARKS

Reconsideration of the present application in view of the preceding amendments and following remarks is respectfully requested. Claims 1-14 are pending and claim 15 is deemed withdrawn as being drawn to nonelected subject matter. Claims 1, 6, 12, and 13 have been amended. Claim 10 has been canceled without prejudice and new claim 16 has been added. Support for the amendments can be found throughout the specification as-filed. For example, support for new claim 16 can be found, in part, on page 15, line 12 to page 16, line 11 as well as previous claim 6. Applicants note the above amendment to the claims and specification were made for clarification purposes only, without prejudice to the filing of any related divisional, continuation, or continuation-in-part application(s). No new matter has been added to the application by way of amendment.

Objections to Oath/Declaration

The Examiner alleges that the oath or declaration is defective. Applicants submit that the Application Data Sheet filed on May 17, 2005 properly lists the mailing address for each named inventor, and thus, no new oath or supplemental ADS is required. Withdrawal of this basis of objection is respectfully requested.

Objections to Specification

The Specification is objected to for the following reasons: i) the specification allegedly fails to cross-reference the priority documents for this application; and ii) the legends to Figures 1-5 on page 9 of the specification do not provide sufficient description for each of the figures. Specifically, the Examiner alleges the figures lack the following details: i) it is unclear which *E. coli* transformants are depicted in lanes 1-4 of Figure 1; ii) Figure 2 lacks a description of the lane contents; iii) Figure 3 lacks a description of the lane contents; iv) Figure does not identify the y-axis; and v) Figure 5 does not describe the origin of sample or how pharmacokinetic analysis was performed.

Applicants submit that 37 C.F.R. §1.73 states that claims to domestic and foreign priority documents may be made in the Application Data Sheet (ADS). Applicants submit that

the ADS filed May 17, 2005 properly claims the benefit of PCT/KR2004/002943, filed 11/13/2004, and foreign application Korea 10-2003-0080299, filed 11/13/2003. However, Applicants, without acquiescence, have amended the specification to properly claim benefit to the above mentioned applications.

Applicants have amended the Brief Descriptions of the Drawings, as described in the Amendments to the Specification section above, and consistent with the descriptions of said figures in Examples 4-6 of the as-filed specification. Accordingly, no new matter has been added by way of this amendment.

Applicants submit that the amendment to Figure 4 consists of labeling the Y-axis as “O.D. (450nm)”, consistent with the description of said figure in Example 5 of the as-filed specification. Accordingly, no new matter has been added by way of this amendment.

Applicants submit that these bases for rejection have been obviated. Withdrawal of these bases for objection is respectfully requested.

Claim rejections under 35 U.S.C. §112, second paragraph

Claims 1-10, 12 and 14 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. Specifically, the Examiner alleges the following: i) claims 1-10, 12, and 14 are indefinite for reciting “*E. coli*-derived signal sequence” because the term “derived” does not have a universally accepted meaning in the art nor is it one which has been adequately defined in the specification; ii) claims 2-5 are indefinite for reciting “and combinations and hybrids thereof” because it is not clear how the constant regions from any one of IgG, IgA, IgM, IgE, or IgD isotypes can be combined into the nucleotide encoding the Ig constant region; iii) claims 6 and 7 are indefinite for reciting “the immunoglobulin region is composed of one to four domains selected from the groups consisting of CH1, CH2, CH3, CH4 and CL domains” because it is not clear how the CL domain can be combined with any one to three of the CH1, CH2, CH3, or CH4 domains to make a constant region; and iv) claim 12 is indefinite for reciting “pSTIIGI_{CHI_3}, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K”

because the expression vectors are referred to by a laboratory designation and the skilled artisan could not determine the full nucleotide sequence or structure for any one of the separate vectors from the claim or reading the specification.

Applicants respectfully traverse these bases for rejection and submit that the present claims are both clear and definite.

Applicants, without acquiescence, have amended claim 1 to recite “an signal sequence isolated from *E. coli*-derived signal sequence”. Applicants submit that support for this amendment may be found in the as-filed specification, for example, on page 18, line 24 to page 19, line 3, and thus, does not constitute new matter. Furthermore, Applicants submit that the Examiner appears to understand the connotation of the phrase “*E. coli*-derived signal sequence” as she uses it in the present Action (e.g., page 16, next to last paragraph).

The Examiner alleges claims 2-5 are indefinite for reciting “and combinations and hybrids thereof” because it is not clear how the constant regions from any one of IgG, IgA, IgM, IgE, or IgD isotypes can be combined into the nucleotide encoding the Ig constant region. Applicants submit that the terms “combination” and “hybrid” are clearly defined on page 10, line 23 to page 11, line 4. One of ordinary skill in the art would recognize that construction of the presently claimed combinations and hybrids comprising immunoglobulin constant regions of the same origin or different origins can be accomplished with well-known recombinant DNA methods (e.g., PCR amplification and DNA cloning). Furthermore, the as-filed specification clearly describes the immunoglobulin constant regions that may comprise said combinations and hybrids (page 11, line 4 to page 12, line 4), and thus, the metes and bounds of claims 2-5 and both clear and definite.

Applicants, without acquiescence, have amended claim 6 to recite “the immunoglobulin region is composed of one to four domains selected from the group[[s]] consisting of CH1, CH2, CH3, and CH4 and CL-domains”. Applicants submit that the as-filed specification is replete with embodiments of such immunoglobulins, and thus, this rejection is rendered moot. However, Applicants have added new claim 16, which recites “the immunoglobulin region comprises a CL domain or one to four domains selected from the group consisting of C_H1, C_H2, C_H3, and C_H4 domains.” Applicants submit that support for this

amendment can be found in the as-filed specification, for example, on page 15, line 12 to page 16, line 11. This passage describes embodiments wherein immunoglobulins may comprise heavy chains, light chains, or heavy and light chains. Additionally, Cox *et al.* (cited by the Examiner) describes growth factor/cytokine fusion proteins that comprise multimers of heavy and light chain fusion proteins; thus, providing evidence that one of ordinary skill in the art readily understands how to combine heavy and light chains in a fusion protein and that such a practice is merely routine in the art.

Applicants, without acquiescence have amended claim 12 to cancel the phrase “pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K”, and thus, this rejection is rendered moot.

Applicants submit that the presents claims are both clear and definite and that one having ordinary skill in the art would readily understand the metes and bounds of the instant claims. Reconsideration and withdrawal of these bases for rejection are respectfully requested.

Biological Deposit Requirement, First Rejection

Claim 12 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner contends that it is unclear if an expression vector having the exact chemical identity of the expression vectors TIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, and pSTIIG4H_K are known and publicly available, or can be reproduced without undue experimentation, and therefore, suggests that a suitable biological deposit be made. Applicants have amended claim 12, which no longer recites said expression vectors. Applicants submit that this basis of rejection has been rendered moot and respectfully request that the Examiner reconsider and withdraw this basis of rejection.

Biological Deposit Requirement, Second Rejection

Claim 13 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner contends that it is

unclear if an *E. coli* transformant having the exact chemical identity of the *E. coli* transformants HMI0927, HMI0928, HMI0929, HMI0930, HMI0931, HMI0932, HMI0933, HMI0934, HMI0935, and HMI0936 are known and publicly available, or can be reproducibly isolated without undue experimentation.

Applicants, without acquiescence, have amended claim 13 to remove HMI0936, and to refer to each transformant by the deposit numbers consistent with the identification of said transformants in the copies of deposit receipts filed with the as-filed specification on May 17, 2005. Furthermore, Applicants have identified the deposit numbers in the as-filed specification (see pages 37, 38, and 42). Thus, it is submitted that the deposits requested by the Examiner have been made and all restriction upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application.

Claim Rejections Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 2-7 stand rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims. Specifically, the Examiner contends that the specification provides enablement for methods of producing Ig constant regions such as: i) IgG, IgA, IgM, IgE, and IgD; ii) IgG1, IgG2, IgG3, and IgG4; and iii) CH1, CH2, CH3, and CH4 or CL; but allegedly does not provide enablement for Ig constant regions that are combinations and hybrids of the foregoing constant regions, or comprising one to four domains of any one of CH1, CH2, CH3, CH4, and CL.

Applicants respectfully traverse this basis of rejection and submit that the as-filed specification provides enables one of ordinary skill in the art to practice the entire scope of the presently claimed invention. As mentioned above, Applicants have amended claim 6 to recite wherein the immunoglobulin constant region is composed of one to four domains selected from the group consisting of C_H1, C_H2, C_H3, and C_H4 domains.

Applicants submit that one of ordinary skill in the art would readily understand how to make and use the presently claimed immunoglobulins. Applicants submit that the present invention is directed, in part, to the mass expression and purification of immunoglobulin constant

regions using a heat-stable enterotoxin II signal sequence, regardless of immunoglobulin function. Contrary to the Examiner's opinion, Applicants submit that the as-filed specification is replete with guidance on how to make the presently claimed immunoglobulin constant region constructs, as evidenced by the numerous embodiments of said constructs described in the Examples. Applicants submit the as-filed specification provides guidance on how the skilled artisan may construct both dimeric and monomeric immunoglobulin constant region constructs (e.g., Example 3). Applicants further submit that only routine experimentation involving DNA cloning and PCR, for example, would be required to construct the presently claimed combinations and hybrids. Example 4 provides guidance on the expression and purification of said constructs. Such methods of making (e.g., cloning) and using (e.g., expressing and purifying the protein in mass quantities) immunoglobulin constant region constructs, combinations, and hybrids may routinely be performed by the skilled artisan and can be accomplished independent of the function of a particular immunoglobulin constant region. Accordingly, Applicants submit that the as-filed specification provides ample guidance on how to carryout the presently claimed methods, and that the skilled artisan would not have to engage in undue experimentation in order to practice the full scope of the claimed invention. Reconsideration and withdrawal of this basis of rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §102(b)

Claims 1, 2, 6, 8, 10, and 14 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Abid-Conquy *et al.* (Protein Engineering 8:859-863 (1995)). Specifically, the Examiner contends that Abid-Conquy *et al.* describe a method for expressing a Fab fragment of a mouse IgM in *E. coli*, wherein the light and heavy chain fragments are cloned into an expression vector; the light chain being fused to a MalE signal sequence of *E. coli* and the heavy chain variable region and first constant region are fused to the alkaline phosphatase signal sequence of *E. coli*. The Examiner further contends that Abid-Conquy *et al.* teach culturing the transformed cell and isolating and purifying the immunoglobulin constant domain in the form of a Fab fragment.

Applicants respectfully traverse this basis for rejection and submit that the disclosure of Abid-Conquy *et al.* fails to anticipate the presently claimed invention because it does not teach each and every limitation of the instant claims. Applicants, without acquiescence, have amended claim 1 to recite “wherein the signal sequence is a heat-stable enterotoxin II signal sequence”.

Applicants submit that Abid-Conquy *et al.* teach the expression and purification of Fab or Fv fragments that are fused to a MalE or PhoA signal sequence and wherein said proteins are secreted into the periplasmic space (page 859, 2nd col., 2nd para.). Applicants submit that Abid-Conquy *et al.* fail to disclose or even suggest that a heat-stable enterotoxin II signal sequence can be fused to immunoglobulin constant regions. In contrast, Applicants presently claim methods to express immunoglobulin constant regions from an expression vector comprising a heat-stable enterotoxin II signal sequence. Applicants submit that the disclosure of Abid-Conquy *et al.* clearly does not teach all the limitations of the presently claimed invention, and thus, fails to anticipate the presently claimed invention. Reconsideration and withdrawal of this basis of rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §102(e)

Claims 1-4, 6-8, and 14 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Capon *et al.* (US 2003/0104535). Specifically, the Examiner contends that Capon *et al.* describe methods for producing immunoadhesions comprising an Ig light and/or heavy chain constant region and signal sequence fusions in order to direct secretion of the Ig fusion molecule, wherein the nucleotides encoding the Ig constant regions and *E. coli* signal peptide are expressed in *E. coli*.

Applicants respectfully traverse this basis for rejection and submit that the disclosure of Capon *et al.* fails to anticipate the presently claimed invention because it does not teach each and every limitation of the instant claims.

Applicants submit that Capon *et al.* teach the expression and purification of immunoadhesions fused to immunoglobulin constant regions and heterologous signal sequences (paragraph 0023). Applicants submit that Capon *et al.* fail to disclose or even suggest that a heat-

stable enterotoxin II signal sequence can be fused to immunoglobulin constant regions. In contrast, Applicants claim methods to express immunoglobulin constant regions from an expression vector comprising a heat-stable enterotoxin II signal sequence. Applicants submit that the disclosure of Capon *et al.* clearly does not teach all the limitations of the presently claimed invention, and thus, fails to anticipate the presently claimed invention. Reconsideration and withdrawal of this basis of rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §103(a), First Rejection

Claims 1-8, 10, and 14 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Cox *et al.* (WO01/03737) in view of Abid-Conquy *et al.* Specifically, the Examiner alleges that Cox *et al.* teach methods for expressing and purifying Ig fusion proteins from expression vectors comprising the Fc domain of antibodies and a signal sequence from a transformed host cell such as a bacterium, but does not specifically teach an *E. coli* signal peptide. The Examiner further alleges that Abid-Conquy *et al.* remedy this deficiency of Cox *et al.* The Examiner contends that one of ordinary skill in the art would have found it *prima facie* obvious to modify the method of Cox *et al.* in view of Abid-Conquy *et al.* to express both light and heavy chain constant domains in-frame with *E. coli* derived signal sequences to express a molecule comprising an Ig constant domain in a transformed prokaryotic cell.

Applicants respectfully traverse this basis of rejection and submit that neither Cox *et al.* nor Abid-Conquy *et al.* alone or in combination establish a *prima facie* case of obviousness against the presently claimed invention, because they do not teach or suggest each and every limitation of the claims. Applicants submit that one of ordinary skill in the art would not find it *prima facie* obvious to modify the teachings of Cox *et al.* in view of Abid-Conquy *et al.* as suggested by the Examiner and arrive at the presently claimed invention.

Applicants submit that the skilled artisan would not reasonably expect to contrive the presently claimed invention over Cox *et al.* in view of Abid-Conquy *et al.* because these references fail to teach an expression vector comprising an immunoglobulin constant region and a heat-stable enterotoxin II signal sequence. Applicants submit that both Cox *et al.* and Abid-Conquy *et al.* disclose methods wherein the fusion proteins described therein are secreted extra-

cellularly or into the periplasmic space. Furthermore, in contrast to the Examiners opinion, Cox *et al.* do not teach any bacterial signal sequences (see page 16, last line Office Action), let alone a heat-stable enterotoxin II signal sequence. Moreover, Abid-Conquy *et al.* also fail to teach an expression vector comprising a heat stable enterotoxin II signal sequence, and thus, fail to remedy this deficiency of Cox *et al.* Thus, Applicants submit that the references cited by the Examiner in combination with the knowledge of the skilled artisan at the time of filing the instant application collectively fail to establish a *prima facie* case against the presently claimed methods, because they do not teach each and every limitation of the claims. Furthermore, Applicants submit that even if the skilled artisan combined the teachings of Cox *et al.* and Adib-Conquy *et al.* as suggested by the Examiner, he would not find it obvious to arrive at the presently claimed invention. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §103(a), Second Rejection

Claims 1 and 9 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Capon *et al.* in view of Sun *et al.* (U.S. Patent No. 6,797,493). Specifically, the Examiner contends that both Capon *et al.* and Sun *et al.* teach generating recombinant Ig constant regions especially IgG4 CH regions based on recombinant techniques. The Examiner further contends the one having ordinary skill in the art would have found it *prima facie* obvious to modify the methods of Capon *et al.* to express the IgG4 constant region of Sun *et al.* and arrive at the presently claimed invention.

Applicants respectfully traverse this basis of rejection and submit that neither Capon *et al.* nor Sun *et al.* alone or in combination establish a *prima facie* case of obviousness against the presently claimed invention, because they do not teach or suggest each and every limitation of the claims. Applicants submit that one of ordinary skill in the art would not find it *prima facie* obvious to modify the teachings of Capon *et al.* in view of Sun *et al.* as suggested by the Examiner and arrive at the presently claimed invention.

Applicants submit that the skilled artisan would not reasonably expect to arrive at the presently claimed invention over Capon *et al.* in view of Sun *et al.* because these references

fail to teach an expression vector comprising an immunoglobulin constant region and a heat-stable enterotoxin II signal sequence. Although Sun *et al.* teach the Ig constant region as set forth in SEQ ID NO: 29, Applicants submit that Sun *et al.* fails to remedy the deficiencies of Capon *et al.*; namely that Capon *et al.* do not teach an expression vector comprising a heat-stable enterotoxin II signal sequence. Thus, Applicants submit that the references cited by the Examiner in combination with the knowledge of the skilled artisan at the time of filing the instant application collectively fail to establish a *prima facie* case against the presently claimed methods, because they do not teach each and every limitation of the claims. Furthermore, Applicants submit that even if the skilled artisan combined the teachings of Capon *et al.* and Sun *et al.* as suggested by the Examiner, he would not find it obvious to arrive at the presently claimed invention. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §103(a), Third Rejection

Claims 1, 10 and 11 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Capon *et al.* in view of Reilly *et al.* (US 2005/0048572). Specifically, the Examiner contends that both Capon *et al.* and Reilly *et al.* teach methods using transformed prokaryotic cells to expressing an Ig constant region and an *E. coli* derived signal peptide and culturing the cells to express the Ig constant region for purification. The Examiner further contends that Reilly *et al.* teach additional signal sequences, including the STII sequence as set forth in SEQ ID NO: 36. The Examiner concludes that one having ordinary skill in the art would have found it *prima facie* obvious to follow the teachings Capon *et al.* to include the *E. coli* derived signal peptide sequences of Reilly *et al.* and have a reasonable expectation of success of arriving at the presently claimed invention.

Applicants respectfully traverse this basis of rejection and submit that neither Capon *et al.* nor Reilly *et al.* alone or in combination establish a *prima facie* case of obviousness against the presently claimed invention. Applicants submit that one of ordinary skill in the art would not find it *prima facie* obvious to produce the presently claimed invention in view of the teachings of Capon *et al.* and Reilly *et al.*

Applicants submit that Capon *et al.* teach the expression and purification of immunoadhesions, as discussed above. Capon *et al.* fail to teach an expression vector comprising a heat-stable enterotoxin II signal sequence. Applicants submit that Reilly *et al.* merely describe a prokaryotic expression system for complete antibodies (see abstract). Reilly *et al.* specifically teach that “a recombinant vector comprises a secretion signal sequence component that directs translocation of the expressed polypeptide across a membrane” (page 16, paragraph 122). Moreover, Reilly *et al.* teach that an expression vector comprising a heat-stable enterotoxin II signal sequence is used for the “periplasmic secretion of heavy and light chains” (page 25, paragraph 216). In contrast, Applicants describe the surprising and unexpected results of an immunoglobulin constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble form; a protein expression strategy that is much more effective than conventional methods based on secreting proteins into the periplasmic space (see as-filed specification, page 26, line 25 to page 28, line 13). Furthermore, Applicants provide experimental evidence supporting the surprising and unexpected cytoplasmic, water-soluble immunoglobulin constant region protein expression (see, e.g., Example 4 and Figure 1).

Applicants submit that one of ordinary skill in the art would not be able to envisage the cytoplasmic, water-soluble protein expression of an immunoglobulin constant region in view of either Capon *et al.* or Reilly *et al.*, especially in view of the fact that Reilly *et al.* teach that antibody heavy or light chains fused to a heat-stable enterotoxin II signal sequence are secreted into the periplasmic space. Thus, even if the skilled artisan combined the teachings of Capon *et al.* and Reilly *et al.* he would not find it obvious to arrive at the presently claimed invention, nor could he, as only the Applicants’ presently claimed methods have been shown to yield cytoplasmic, and not periplasmic, water-soluble protein expression of immunoglobulin constant regions.

Accordingly, Applicants submit that the references cited by the Examiner have failed to establish a *prima facie* case of obviousness against the presently claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §103(a), Fourth Rejection

Claims 1, 10 and 11 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Capon *et al.* in view of Reilly *et al.*, in further view of Kwon *et al.* (U.S. Patent No. 6,605,697). Specifically, the Examiner contends that Kwon *et al.* teach additional STII peptides as set forth in SEQ ID NOs: 36-46, and that it would have been *prima facie* obvious for the skilled artisan to following the teachings of Capon *et al.* and Reilly *et al.* to include the *E. coli* derived signal peptide sequences of Kwon *et al.* and have a reasonable expectation of success of arriving at the presently claimed invention.

Applicants respectfully traverse this basis of rejection and submit that neither Capon *et al.*, Reilly *et al.*, nor Kwon *et al.* alone or in combination establish a *prima facie* case of obviousness against the presently claimed invention. Applicants submit that one of ordinary skill in the art would not find it *prima facie* obvious to produce the presently claimed invention in view of the teachings of Capon *et al.*, Reilly *et al.*, and Kwon *et al.*

Applicants submit that the teachings of Capon *et al.* and Reilly *et al.* are discussed above. Applicants further submit that Kwon *et al.* merely describe additional heat-stable enterotoxin II signal sequences with enhanced secretion efficiency into the periplasmic space (see abstract and column 2, lines 34-38). Thus, Kwon *et al.* fail to remedy the deficiencies of Capon *et al.* and Reilly *et al.* Applicants submit that neither of these three references provide for the presently claimed methods of producing an immunoglobulin constant region using an expression vector comprising a heat-stable enterotoxin II signal sequence that results in the unexpected and surprising cytoplasmic and water-soluble protein expression of said immunoglobulin constant region. Thus, Applicants submit that the skilled artisan would not find it obvious to arrive at the presently claimed invention in view of Capon *et al.*, Reilly *et al.*, and Kwon *et al.*, as only the Applicants' presently claimed methods have been shown to yield cytoplasmic, and not periplasmic, water-soluble protein expression of immunoglobulin constant regions.

Accordingly, Applicants submit that the references cited by the Examiner have failed to establish a *prima facie* case of obviousness against the presently claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



William T. Christiansen, Ph.D.
Registration No. 44,614

WTC:jto

Enclosure:

1 Sheet of Drawing (Figure 4)
701 Fifth Avenue, Suite 5400
Seattle, Washington 98104
Phone: (206) 622-4900
Fax: (206) 682-6031

1166154_1.DOC